

Impact of Comorbidities on Risk of Cardiovascular Hospitalization and All-cause Mortality Among Patients With and Without Atrial Fibrillation in an Integrated Health System

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Disclosures

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Burden and Public Health Impact of Atrial Fibrillation

- **Estimated US prevalence of atrial fibrillation (AF) or atrial flutter (AFL): 2.7–6.1 million (2010); expected to rise to ~5.6–12 million by 2050¹**
- **AF patients frequently have cardiovascular (CV) comorbidities and are at increased risk for hospitalization^{2,3}**
 - ~ 467,000 hospitalizations per year in the US are attributed to AF/AFL¹
- **CV hospitalization (CVH) is also associated with decreased quality of life^{4,5} and increased risk of mortality^{1,6}**
 - AF was mentioned on 99,294 US death certificates and was the underlying cause in 15,383 of those deaths in 2008¹
- **There are limited data characterizing conditions known to be risk factors for AF and those that develop as a consequence of AF, including the incidence of CVH**

Study Objectives

- To assess the impact of AF, baseline comorbidity burden, CV events, and persistence on risk of CVH among patients on first-line therapies
- To assess prevalence of comorbidities at baseline and incidence of new CV events or new morbidities among newly diagnosed AF patients compared with demographically matched non-AF patients

Methods

● Design

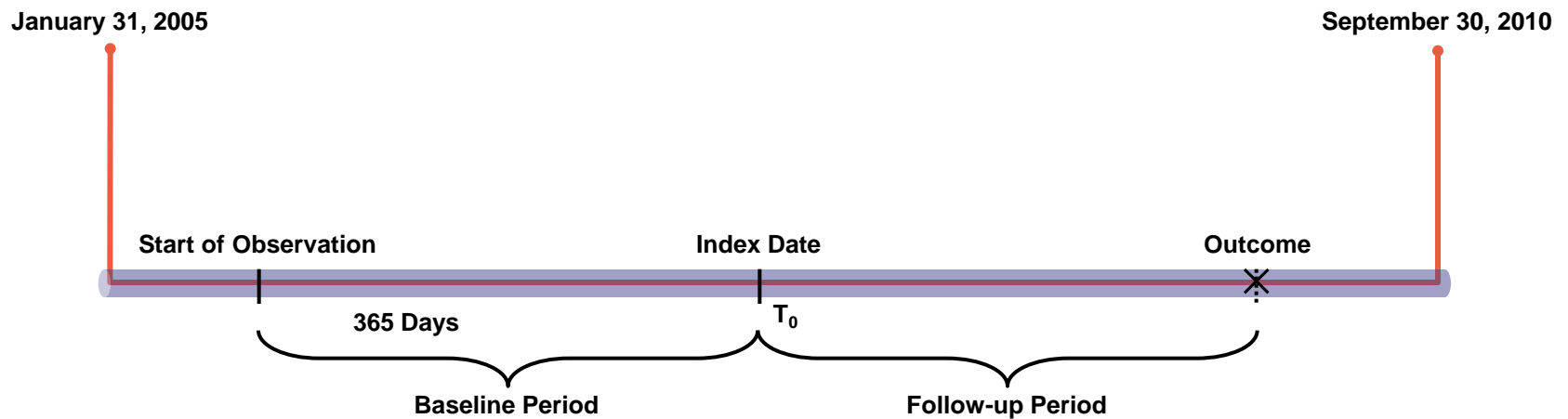
- Retrospective, comparative cohort study of newly diagnosed AF patients (cases) and demographically similar controls (non-AF patients)
 - Characterize the impact of existing and newly occurring comorbidities on risk of CVH and all-cause mortality among AF vs. non-AF patients

● Data Source

- Electronic medical record (EMR) data (1/31/2005–9/30/2010)
- MedMining EMR data contain ~3.8 million patients receiving care from the Geisinger Health System
- Data include both inpatient and outpatient settings
 - Primary care, specialty care, inpatient encounters (including discharge diagnoses), procedures, selected laboratory results, medication orders (including dose, frequency, and reason for discontinuation)
 - Information on patient demographics

Study Design

- **Index date: defined by first inpatient or second outpatient diagnosis**
- **Defined baseline and follow-up periods**
 - **Baseline period:** defined as 364 days prior to the index date and ending on the index date; data used to obtain information about each patient's medical history and baseline comorbidities
 - **Follow-up period:** defined as the day after the index date and ending after occurrence of study end point, when the patient exited the database, or on the study end date (whichever came first); data used to assess the risk of new CV events, new morbidities, and hospitalizations



Patient Selection

INCLUSION CRITERIA

- AF patients MUST have had at least 2 outpatient diagnoses of AF within 30 days with ICD-9-CM codes of 427.31 (AF) or 427.32 (AFL) or at least 1 hospitalization for AF during baseline (or pre-index) period
- Non-AF patients (comparators) were matched for age in 5-year categories and by gender

EXCLUSION CRITERIA

- <40 years of age at index date
- ICD-9-CM codes relating to cardiac surgery within 364 days of the index date or related to hyperthyroid disease or valvular disease within 90 days of the index date*
- <1 day of follow-up
- <364 continuous baseline days in the database

Patient Disposition

Total enrollees from January 31, 2005–September 30, 2010
N=33,844

1 inpatient or 2 outpatient diagnoses within 30 days
n=16,102 (Excluded: n=17,742 [52.4%])

Aged ≥ 40 years, ≥ 1 day of follow-up, ≥ 365 day baseline period
n=10,605 (Excluded: 5,497 [34.1%])

No cardiac surgery in 365 days of baseline and hyperthyroidism or
valvular disease within 90 days of baseline
n=7,791 (Excluded: 2,814 [26.5%])

AF Patient Cohort:
n=3,919

Matched Non-AF Patient Cohort:
n=3,872

Baseline Patient Characteristics: Groups were similar with regard to age, gender, and race; comorbidities were more common among AF patients

Characteristic	AF Patients (n=3,919)	Non-AF Patients (n=3,872)
Index AF diagnosis, n (%)		
Inpatient	1,940 (49.4)	—
Outpatient	1,979 (50.4)	—
Duration of follow-up, y, mean (SD)	1.87 (1.36)	1.96 (1.45)
Age, y, mean (SD); median	72.7 (11.5); 75.0	71.1 (11.2); 73.0
Gender, n (%)		
Male	2,071 (52.8)	2,199 (56.8)
Female	1,848 (47.1)	1,673 (43.2)
Race, n (%)		
White/Caucasian	3,883 (98.9)	3,789 (97.9)
African American	19 (0.5)	16 (0.4)
Other*	17 (0.4)	67 (1.7)
Medications, n (%)		
β-blockers	2,678 (68.2)	907 (23.4)
Calcium channel blockers	1,385 (35.3)	380 (9.8)
Digoxin	740 (18.8)	60 (1.5)
Anticoagulants	2,339 (59.6)	229 (5.9)
Charlson Comorbidity Index†		
0-1	1,592 (40.6)	2,772 (71.6)
2-3	1,167 (29.7)	876 (22.6)
≥4	1,160 (29.5)	224 (5.8)

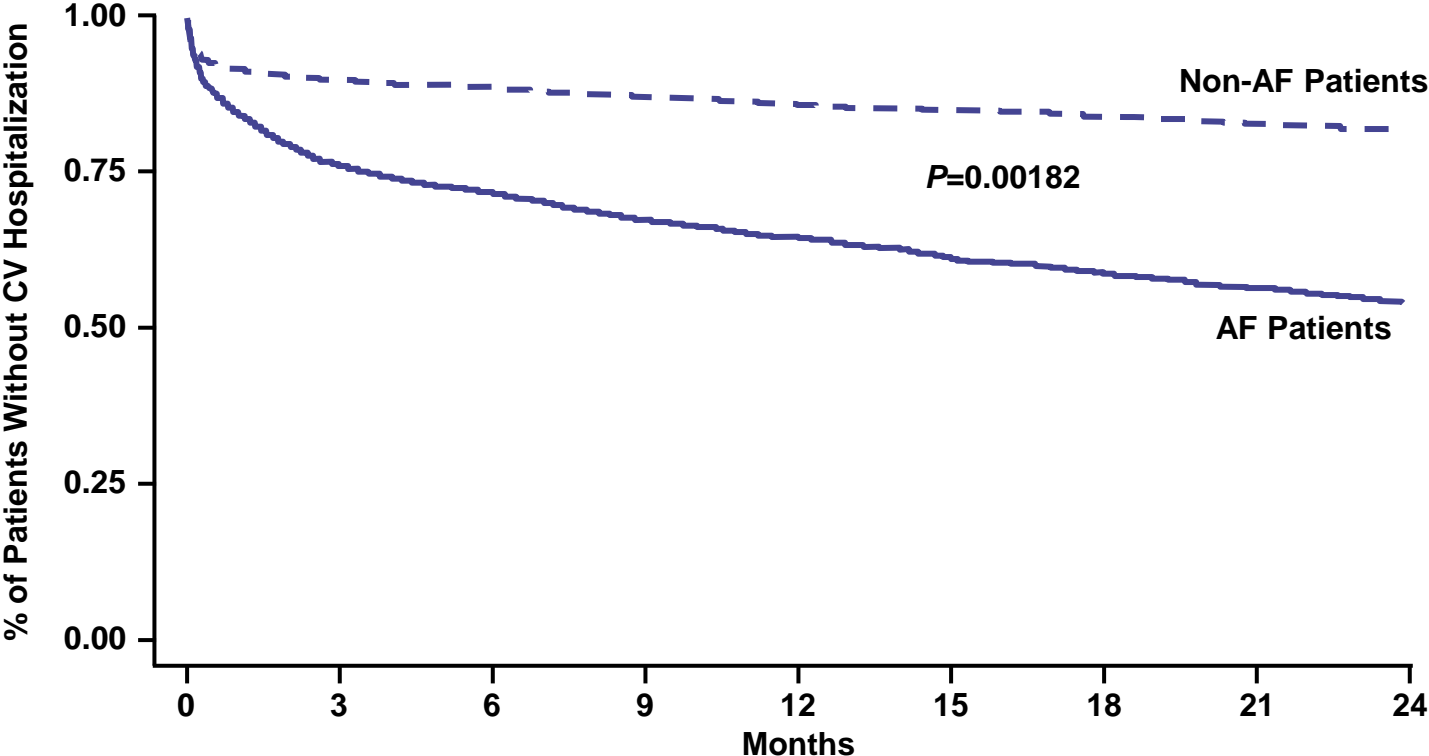
Baseline Comorbidity Prevalence*: Most of the 15 selected comorbidities were higher among AF patients

Comorbidities, n (%)	AF Patients (n=3,919)	Non-AF Patients (n=3,872)	OR (95% CI)
Myocardial infarction	98 (2.5)	3 (0.1)	33.08 (10.97–163.24)
Heart failure	927 (23.7)	56 (1.4)	21.11 (16.03–28.28)
Cardiac hypertrophy	358 (9.1)	16 (0.4)	24.23 (14.67–42.93)
Valvular heart disease	110 (2.8)	7 (0.2)	15.50 (7.25–39.52)
Sleep apnea	280 (7.1)	25 (0.6)	11.84 (7.83–18.65)
Pulmonary embolism	125 (3.2)	11 (0.3)	11.56 (6.23–23.79)
Hypertension	2,720 (69.4)	645 (16.7)	11.35 (10.20–12.70)
Coronary heart disease	1,279 (32.6)	225 (5.8)	7.85 (6.74–9.15)
COPD	681 (17.4)	107 (2.8)	7.40 (5.99–9.21)
Syncope	249 (6.4)	43 (1.1)	6.04 (4.34–8.58)
Stroke	814 (20.8)	203 (5.2)	4.74 (4.02–5.58)
Diabetes	1,114 (28.4)	302 (7.8)	4.69 (4.09–5.39)
Obesity	1,428 (36.4)	549 (14.2)	3.47 (3.10–3.88)
Major bleeding	1,091 (27.8)	423 (10.9)	3.15 (2.78–3.56)
Hyperthyroidism	16 (0.4)	9 (0.2)	1.76 (0.73–4.52)

New CV Events and New Morbidities During the Follow-up Period: The incidence was higher among AF patients, with heart failure having the highest RR (>4)

New CV Events & Morbidities, n (%)	AF Patients (n=3,919)		Non-AF Patients (n=3,872)		RR (95% CI)
	# of Cases	Rate (per 1,000 PYs)	# of Cases	Rate (per 1,000 PYs)	
Heart failure	663	140.20	234	33.12	4.23 (3.64–4.94)
Cardiac hypertrophy	471	77.85	166	22.94	3.39 (2.84–4.08)
Valvular heart disease	713	121.96	303	42.83	2.85 (2.49–3.27)
Pulmonary embolism	96	13.96	45	6.08	2.30 (1.60–3.35)
Major bleeding	1,128	315.93	779	140.09	2.26 (2.06–2.47)
Coronary heart disease	560	137.29	487	76.43	1.80 (1.59–2.03)
Stroke	540	104.18	418	63.37	1.64 (1.44–1.87)
Myocardial infarction	107	15.39	79	10.70	1.44 (1.06–1.95)

Time to Cardiovascular Hospitalization (CVH): CVH risk was higher in AF patients, occurred early, and persisted during the 24-month follow-up observation period



AF Patients	3,919	2,724	2,332	2,005	1,758	1,536	1,341	1,150	994
Non-AF Patients	3,872	3,033	2,704	2,486	2,277	2,086	1,894	1,692	1,513
Number of Patients Remaining at Each Quarterly Interval									

All-cause Mortality & CVH During the Post Index Time Period: All-cause mortality and hospitalization was higher among AF patients

Outcomes	AF Patients (n=3,919)			Non-AF Patients (n=3,872)			RR (95% CI)
	n	Rate (per 1,000 PYs)	PYs	n	Rate (per 1,000 PYs)	PYs	
All-cause mortality	203	28.1	7,215	144	19.3	7,469	1.46 (1.17–1.82)
CVH or all-cause mortality	1,721	353.6	4,867	731	110.0	6,645	3.21 (2.95–3.51)
CVH	1,661	341.2	4,867	667	100.4	6,645	3.40 (3.11–3.72)

Strengths & Limitations

● Strengths

- EMR were derived from source data reflecting medical practice
- Validated coding algorithms were utilized to identify conditions, if they were available

● Limitations

- This EMR database represents a narrow geographic region (central Pennsylvania)
- Healthcare varies by geographic region; thus, patterns of care observed in this study may not be generalizable to the entire country
- ECGs were not obtained; recorded AF diagnoses using ancillary clinical data were not confirmed

Conclusions

- **AF patients had a higher severity of illness (Charlson Comorbidity Index score ≥ 4) and a higher prevalence of pre-existing comorbidities**
- **The incidence of new CV events and new morbidities during the follow-up period was higher among AF patients, with heart failure having the highest RR (>4)**
- **Among AF patients, 25.3% experienced recurrent AF requiring hospitalization**
 - CVH risk was higher in AF patients, occurred early, and persisted during the 24-month follow-up observation period
- **All-cause mortality & CVH during the post-index time period was higher among AF patients**
- **AF management and treatment remains an important unmet clinical need as evidenced by:**
 - High prevalence of chronic comorbidities at the time of AF diagnosis

BACK UP SLIDES

First-line AF Therapy Among Newly Treated AF Cohort

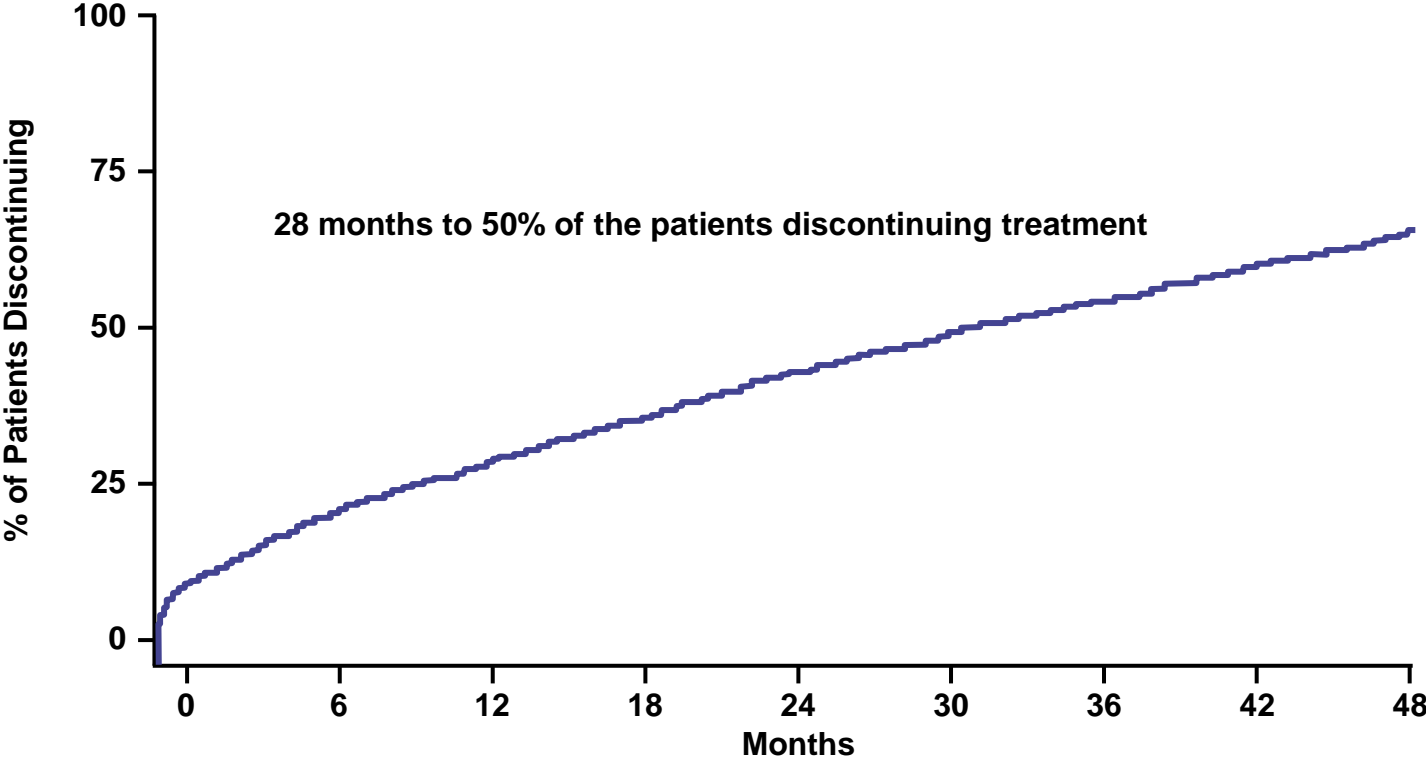
AF-related Therapy	AF Patients	Duration on Treatment (Days)	
		Mean (SD)	Median (Range)
	n (%)		
First-line therapy	1,636 (100.0)	942.4 (708.0)	883.0 (1–2,066)
Rate control	1,402 (85.7)	946.1 (710.1)	887.5 (1–2,066)
Class II – β -blockers	950 (58.1)	949.2 (714.4)	881.5 (1–2,066)
Class IV – calcium channel blockers	94 (5.7)	615.9 (637.4)	439.5 (1–2,055)
Digoxin	358 (21.9)	1024.7 (639.9)	1042.5 (1–2,039)
Rhythm control	234 (14.3)	919.8 (696.1)	859.5 (1–2,054)
Class III – potassium channel blockers	107 (6.5)	794.8 (656.5)	680.0 (1–2,032)
Class I – sodium channel blockers	43 (2.6)	956.5 (671.1)	977.0 (1–1,996)
Sotalol	84 (5.1)	1,060.3 (735.5)	1,123.5 (1–2,054)

Treatment Discontinuations on First-line Therapy Among Newly Treated AF Cohort*

AF-related Therapy	AF Patients	Duration on Treatment (Days)	
		Mean (SD)	Median (Range)
First-line therapy	779 (100.0)	808.2 (718.5)	631 (1–2,065)
Rate control	685 (87.9)	804.1 (717.8)	620 (1–2,065)
Class II – β -blockers	502 (64.4)	836.0 (723.1)	680.5 (1–2,065)
Class IV – calcium channel blockers	39 (5.0)	454.0 (603.4)	206 (1–1,939)
Digoxin	144 (18.5)	787.7 (706.3)	556.5 (1–2,029)
Rhythm control	94 (12.1)	837.8 (726.8)	707.5 (1–2,028)
Class III – potassium channel blockers	39 (5.0)	639.0 (647.0)	285 (1–2,028)
Class I – sodium channel blockers	15 (1.9)	617.6 (637.7)	341 (1–1,793)
Sotalol	40 (5.1)	1,114.2 (754.6)	1,410 (1–2,010)

*Discontinuation does not include patients who switched.

Time to AF Drug Discontinuation Among Newly Treated AF Patients



Newly Treated	1,636	1,275	1,146	1,027	903	809	719	625	639
Number of Patients Remaining at Each 6-month Interval									

Treatment Switches Among Patients Who Discontinued First-line Therapy Among Newly Treated AF Cohort

AF-related Therapy	n	Treatment Switched to:	
		Rate Control n (%)	Rhythm Control n (%)
Treatment Initiated	n	n (%)	n (%)
Rate control	1,402	118 (8.4)	25 (1.8)
Class II – β -blockers	950	78 (8.2)	22 (2.3)
Class IV – calcium channel blockers	94	14 (14.9)	1 (1.1)
Digoxin	358	26 (7.3)	2 (0.6)
Rhythm control	234	29 (12.4)	8 (3.4)
Class III – potassium channel blockers	107	16 (15.0)	1 (0.9)
Class I – sodium channel blockers	43	1 (2.3)	2 (4.7)
Sotalol	84	12 (14.3)	5 (6.0)

Class II – β -blockers included: atenolol, esmolol, metoprolol, nadolol, pindolol, propranolol.

Class IV – Calcium channel blockers included: diltiazem, verapamil.

Class III – Potassium channel blockers included: amiodarone, dofetilide, ibutilide.

Class I – Sodium channel blockers included: disopyramide, flecainide, procainamide, propafenone, quinidine.

Select Causes of CVH*: Each category of CVH occurred more frequently among AF patients than comparators

Causes	AF Patients (n=3,919)			Non-AF Patients (n=3,872)			RR (95% CI)
	# of Cases	Rate (per 1,000 PYs)	PYs	# of Cases	Rate (per 1,000 PYs)	PYs	
AF and AFL	993	169.6	5,857	0	0	7,469	INF (342.70–INF)
Cardiac dysrhythmias	1,167	207.1	5,635	163	22.4	7,284	9.25 (7.85–10.97)
Heart failure	517	78.1	6,621	104	14.1	7,353	5.52 (4.46–6.88)
Ventricular arrhythmia or cardiac arrest	94	13.2	7,139	23	3.1	7,446	4.26 (2.68–7.05)
Cerebrovascular disease	417	61.6	6,765	224	31.0	7,216	1.99 (1.68–2.35)
Coronary heart disease	356	52.8	6,737	192	26.7	7,191	1.98 (1.66–2.37)
Hypertensive disease	142	20.2	7,038	78	10.6	7,348	1.90 (1.43–2.54)
Acute and subacute coronary syndrome	132	18.7	7,058	80	10.9	7,372	1.72 (1.30–2.30)
Acute myocardial infarction	75	10.5	7,145	53	7.2	7,409	1.47 (1.02–2.13)

All-cause Mortality Stratified by Baseline Comorbidity: All-cause mortality was highest among AF patients with MI

Comorbidity	AF Patients With Comorbidity			Non-AF Patients Without Comorbidity			RR (95% CI)
	# of Cases	PYs	Rate (per 1,000 PYs)	# of Cases	PYs	Rate (per 1,000 PYs)	
Myocardial infarction	19	152	124.73	184	7,062	26.05	4.79 (2.82–7.69)
Heart failure	87	1,564	55.64	116	5,651	20.53	2.71 (2.03–3.61)
Cardiac hypertrophy	36	550	65.51	167	6,665	25.06	2.61 (1.77–3.77)
Stroke	73	1,358	53.76	130	5,857	22.20	2.42 (1.79–3.25)
Coronary heart disease	95	2,312	41.09	108	4,903	22.03	1.87 (1.40–2.48)
Major bleeding	78	1,952	39.95	125	5,262	23.75	1.68 (1.25–2.25)
Valvular heart disease	9	238	37.78	194	6,977	27.81	1.36 (0.61–2.63)
Pulmonary embolism	8	236	33.89	195	6,979	27.94	1.21 (0.52–2.44)

CVH Stratified by Baseline Comorbidity: The rate of CVH was highest among patients with a previous MI

Comorbidity	AF Patients With Comorbidity			Non-AF Patients Without Comorbidity			RR (95% CI)
	# of Cases	PYs	Rate (per 1,000 PYs)	# of Cases	PYs	Rate (per 1,000 PYs)	
Myocardial infarction	58	80	723.46	1,603	4,787	334.84	2.16 (1.63–2.81)
Cardiac hypertrophy	190	308	616.65	1,471	4,559	322.63	1.91 (1.63–2.22)
Heart failure	489	910	537.33	1,172	3,957	296.15	1.81 (1.63–2.02)
Stroke	406	825	492.35	1,255	4,043	310.42	1.59 (1.41–1.78)
Pulmonary embolism	70	134	522.45	1,591	4,734	336.11	1.55 (1.21–1.98)
Valvular heart disease	70	136	515.80	1,591	4,732	336.24	1.53 (1.19–1.95)
Coronary heart disease	633	1,421	445.46	1,028	3,446	298.28	1.49 (1.35–1.65)
Major bleeding	524	1,223	428.50	1,137	3,645	311.97	1.37 (1.24–1.52)

All-cause Mortality & CVH Stratified by Baseline Comorbidity: MI was most strongly associated with CVH and mortality

Comorbidity	AF Patients With Comorbidity			Non-AF Patients Without Comorbidity			RR (95% CI)
	# of Cases	PYs	Rate (per 1,000 PYs)	# of Cases	PYs	Rate (per 1,000 PYs)	
Myocardial infarction	64	80	798.31	1,657	4,787	346.12	2.31 (1.77–2.96)
Cardiac hypertrophy	199	308	645.86	1,522	4,559	333.82	1.93 (1.66–2.24)
Heart failure	516	910	566.99	1,205	3,957	304.49	1.86 (1.68–2.07)
Stroke	426	825	516.60	1,295	4,043	320.32	1.61 (1.44–1.80)
Pulmonary embolism	72	134	537.37	1,649	4,734	348.37	1.54 (1.20–1.95)
Coronary heart disease	663	1,421	466.57	1,058	3,446	306.98	1.52 (1.38–1.68)
Valvular heart disease	71	136	523.16	1,650	4,732	348.71	1.50 (1.17–1.90)
Major bleeding	542	1,223	443.22	1,179	3,645	323.49	1.37 (1.24–1.52)